Epidemiological data indicate that tobacco smoking, beside strong dependence, causes a number of cancers and diseases of the respiratory, digestive and cardiovascular systems. However, despite the known health risks, a smoker lights up another cigarette to relax, for better concentration, to decrease their appetite, improve digestion, alleviate stress symptoms or finally to improve mood.

Currently, there is no ideal prescription that would help all tobacco smokers in quitting smoking. Current pharmacotherapies for nicotine addiction include agents containing pure nicotine (nicotine replacement therapy – chewing gums, transdermal patches, lozenges, nasal sprays or inhalers), or other drugs acting at cholinergic system (varenicline and cytisine), antidepressants (bupropion or nortriptyline), or hypotensive drug clonidine. Since these pharmacotherapies exert many side effects and are not effective for all smokers, there is still an urgent need for developing new treatment strategies for nicotine addiction.

Quitting smoking is challenging. Smokers are worried about how they will cope during the first days/weeks of quitting due to the unpleasant withdrawal symptoms such as craving, irritability, increased appetite or depression. Very often, attempts to quit smoking fail. Meanwhile, if the smokers would be provided with attractive therapy – supported by non-pharmacological methods – maybe they would more willingly decide on this difficult step.

Current research studies concentrate on finding new strategies that alleviate nicotine craving and depression symptoms during the abstinence period. Researchers found that tissue level of serotonin – a neurotransmitter that seems to be associated with depression – is reduced in laboratory animals withdrawn from nicotine. Recently, it has been shown that stimulation of serotonin receptors in the brain induces antidepressant-like effects, and furthermore, attenuates some of the symptoms of nicotine dependence in rodents.

Another important goal of many research groups is to identify the mechanisms that induce smoking relapse through the negative withdrawal symptoms. Recent findings indicate that nicotine self-administration impairs neurogenesis in the hippocampus of adult rats, a process of generation of new neurons in the adult brain. Since deteriorations in neurogenesis in the above mentioned brain region seem to be associated with depression, it can be speculated that impairments of this process in animals after nicotine may contribute to the depressive symptoms occurring during drug withdrawal, and their reversal would prevent reinstatement to drug-seeking behaviour. Interestingly, the aforementioned activators of serotonin receptors potentiate the neurogenesis process in rodents and, therefore, it can be speculated that administration of these compounds during nicotine withdrawal would alleviate not only depressive symptoms, but possibly reverse changes in neurogenesis induced by nicotine withdrawal.

The aim of the proposed project is to investigate, whether the drugs stimulating serotonin receptors during nicotine withdrawal modulate depressive-like effects characteristic for this period, and reinstatement to drug-seeking behaviour. It is planned to investigate whether withdrawal from nicotine self-administration induces changes in the process of generation of new neurons in the hippocampus of adult rats and whether tested compounds modulate these effects. The animal group with access to the running wheels will serve as a positive control in the behavioral and cellular studies. Based on the literature data, exercise, such as wheel running in rodents during nicotine withdrawal attenuates the reinstatement of drug-seeking behaviour, and at the cellular level, increases the neurogenesis process. Using the neurogenesis inhibitor, it will be examined whether the inhibition of neurogenesis affects reinstatement and whether the effect of activation of serotonin receptors on animals' behavior is related to its effects on neurogenesis.

In the project, a model of intravenous nicotine self-administration in rats will be used. It is one of the best animal models that mirrors nicotine addiction in humans. Serotonin compounds will be administered during withdrawal from nicotine self-administration, and the behavior of animals will be then evaluated in the tests used to study depression, i.e. the sucrose preference test and the resignation test. Reinstatement of drug-seeking behavior will be induced by nicotine administration or exposure to the environmental stimulus associated with previous nicotine intake. Different stages of neurogenesis will be examined using immunohistochemistry and immunofluorescence methods.

Research results obtained in this project may find new treatment strategy for nicotine addiction in humans and extend knowledge about the molecular mechanisms that trigger nicotine-seeking behaviour.